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Food and Drug Administration

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SACCHARIN AND ITS SALTS

Proposed Rule and Hearing

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 145, 150, 172, 180, 189, 310, 430, 510, 589, and 700]

[Docket No. 77N-0085]

SACCHARIN AND ITS SALTS

Proposed Rule Making

AGENCY: Food and Drug Administration

ACTION: Proposed rule.

SUMMARY: The Commissioner of Food and Drugs is proposing to revoke the interim food additive regulation under which saccharin and its salts (saccharin) are currently permitted as ingredients in prepackaged foods, such as soft drinks, and as tabletop nonnutritive sweeteners. The Commissioner is also inviting comments on a proposal to accept and promptly review new drug applications for the marketing of saccharin as a single-ingredient drug, available without a physician's prescription. If approvable under the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), such products would be required to bear a conspicuous warning about the risk of cancer. The Commissioner is also proposing to prohibit the use of saccharin in cosmetics that are likely to be ingested, to amend the standards of identity that provide for the use of saccharin and to prohibit the use of saccharin in animal drugs and animal feed.

The Commissioner's determination that saccharin must be banned as a food additive is based on a series of scientific studies conducted in accordance with currently accepted methods for determing whether compounds can cause cancer. The most recent of these studies, conducted by Canadian scientists under the auspices of the Canadian Government, confirms what earlier American studies have suggested: that saccharin poses a significant risk of cancer for humans. Under these circumstances, conscientious concern for the public health requires that FDA prohibit the continued general use of saccharin in foods.

This conclusion is also dictated by the so-called Delaney clause of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)(3)), which prohibits the use in food of any food additive which has been shown, by ingestion or other appropriate tests, to cause cancer in laboratory animals.

The Delaney clause does not apply to human drugs, however, and it therefore does not prohibit the approval of a drug that has been shown to ca cancer in laboratory animals if the drug provides medical benefits that outweight the potential risk. For many individuals, including diabetics who must limit their intake of sugar and other carbohydrates, the availability of a nonnutritive sweetener, may serve a legitimate medical need. The Commissioner is therefore proposing to permit the submission of new drug applications for the marketing of saccharin as a single-ingredient OTC drug, which applications must be accompanied by legally sufficient evidence of the effectiveness of saccharin for its labeled indications.

DATES: Comments on this proposal may be submitted by June 14, 1977. Published elsewhere in this issue of the FEDERAL REGISTER is a notice of an informal hearing before the Commissioner to be held on May 18 and 19, 1977 to hear oral comments on this proposal.

ADDRESS: Written comments should be sent (preferably in quadruplicate) to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

GENERAL: Ronald J. Wylie, Compliance Regulations Policy Staff (HFC-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3480.

FOODS: John J. McAuliffe, Bureau of Foods (HFF-334), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, DC 20204, 202-472-5690.

HUMAN DRUGS: Paul Fehnel, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3640.

COSMETICS: Heinz Eiermann, Bureau of Foods (HFF-440), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204, 202-245-1530.

VETERINARY DRUGS: Edward Ballitch, Bureau of Veterinary Medicine (HFV-231), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3336.

SUPPLEMENTARY INFORMATION:

I. SACCHARIN AS A FOOD INGREDIENT

A. HISTORY OF THE USE AND SAFETY OF SACCHARIN

Saccharin is a nonnutritive, artificial sweetener that is approximately 350 times sweeter than sugar. Following the discovery of saccharin in 1879, commercial interest was initially shown in its possible usefulness as an antiseptic or as a preservative to inhibit fermentation in foods, but from the beginning, questions about its safety existed. In 1886, workers in Europe noted no effects in human subjects who had been given single doses of saccharin up to 5 grams. In 1888, a French scientist reported no harmful effects in diabetics who ingested 5 grams per day for 5 months. During the succeeding decade, several reports both endorsing and criticizing the use of saccharin in diabetics noted evidence in some patients of loss of appetite, nausea, and pressure in the stomach. In the meantime, attempts to use saccharin in the treatment of intestinal infections, chronic gastritis, cystitis, and numerous other diseases proved unsuccessful. By 1907, however, canners of fruits and vegetables in the United States had developed an interest in using saccharin to sweeten their products. In 1912, a Board of Scientific Advisors to the Secretary of Agriculture, appointed by President Theodore Roosevelt, concluded that 0.3 gram/day of saccharin was safe and that higher levels of intake, especially above 1 gram/day, caused disturbances of digestion.

In numerous toxicological studies in experimental animals during the period 1920 to 1950, no findings were reported that raised serious questions about the safety of saccharin as then used. In Europe, during World Wars I and II, the consumption of saccharin greatly increased, with no apparent adverse effects among consumers, though no adequate epidemiologic studies were conducted at that time.

Saccharin use today is widespread. Approximately 6 to 7.6 million pounds of saccharin were used in the United States in 1976. It is used in food and beverages, cosmetics, drugs, animal feed, and industrial processes. Food and beverage uses are by far the most extensive, accounting for over 70 percent of the saccharin used.

The soft drink industry accounts for about 74 percent of the saccharin consumed in food and beverages in the United States. Other dietary uses, which account for 14 percent of the saccharin consumed, include powdered juices and drinks, other beverages, sauces and dressings, canned fruits, dessert toppings, cookies, gums, jams, candies, ice cream, and puddings. About 12 percent of the saccharin consumed is as a sweetener in place of nutritive sweeteners (e.g., sugar) in coffee and tea and on cereal.

Although saccharin's predominant use is in foods, it is also used in drugs—both prescription and OTC—especially those intended for pediatric use and for use by diabetics. Saccharin is also found in a variety of cosmetics, including lipsticks, dentifrices, mouthwashes, aftershave lotions, moisturizing skin preparations, hair tonics, skin cleansers, bubble baths, colognes, face powders, and douches. Saccharin is also used to a limited extent in animal feed and animal drugs.

One of the first chronic toxicity studies of saccharin was reported by Fitzhugh et al. in 1951 (discussed below). The findings of that study were inconclusive and there continued to be debate among scientists about the safety of saccharin. Accordingly, in 1955 the Committee on Food Protection of the National Academy of Sciences reviewed the literature bearing on the safety of saccharin and concluded that the "maximum probable tolerance level for saccharin in the human diet is at least as great as 1.0 gram per day." The National Academy of Sciences (NAS) committee further concluded that the substitution of saccharin for the average daily consumption of sugar in the United States would amount to about 0.3 gram of saccharin, and that

"the maximal amount of saccharin likely to be consumed was not hazardous."

Because of greatly increased use of saccharin and cyclamate, another nonnutritive sweetener, as well as drastic changes in the patterns of their consumption during the 1960's, in 1967 FDA requested the National Academy of Sciences again to evaluate the safety of these nonnutritive sweeteners. In response to this request, an ad hoc committee was formed under the NAS Committee on Food Protection. In 1968, the committee issued an interim report in which it concluded that the intake of 1 gram or less per day of saccharin by an adult should present no hazard. However, the committee also recognized at that time that the existing carcinogenesis studies on saccharin, judged by current standards, were inadequate, and it therefore recommended that contemporary studies be undertaken.

During the late 1960's, saccharin was being widely used competitively or in combination with cyclamates. Consequently, when the use of cyclamate was banned by FDA in 1969, it was anticipated that the daily intake of saccharin by users of nonnutritive sweeteners would increase substantially. An ad hoc subcommittee of the NAS Committee on Food Protection was once again requested by FDA to review all available toxicity data on saccharin in the light of the projected sharp increase in use.

The NAS subcommittee issued its final report in July 1970. It arrived at conclusions regarding the safety of saccharin very similar to the assessments of 1955 and 1968. The subcommittee again recommended that chronic toxicity studies, designed according to modern protocols, be completed. It further recommended that: (a) epidemiologic studies should be carried out with emphasis on the diabetic segment of the population and in relation to pregnancy; (b) comparative metabolism studies should be done in man and in animals; and (c) toxicologic interactions with other selected chemicals should be explored.

Although the then existing studies raised some questions about whether saccharin could cause cancer, no firm conclusions could be reached on the basis of those data. In 1972, because of the questions about the safety of saccharin, FDA removed saccharin from the list of substances generally recognized as safe (GRAS) and imposed limits on the use of saccharin to discourage general use by consumers and to inhibit an increase in its use by the general population. At that time, FDA also issued an interim food additive regulation to permit continued limited use of saccharin pending completion of studies to resolve the questions concerning the safety of saccharin. In issuing the interim regulation, FDA concluded that the continued limited use of saccharin did not constitute a significant risk to public health.

B. HISTORY OF SCIENTIFIC AND MEDICAL INQUIRY INTO THE CAUSES OF CANCER

Sir Percival Potts' description, almost 200 years ago, of the relationship between exposure to soot and cancer of the scrotum in chimney sweeps is usually cited as marking the beginning of studies in environmental carcinogenesis (Ref. 1). It was not until the late 19th century, however, that the association between exposure to aromatic amines and the production of bladder cancer among workers in the German dye industry was established, and only in the early part of this century that the production of skin cancer by X-radiation and radium became evident.

Modern research on chemical carcinogenesis dates from the classic studies of Yamagiwa and Itchikawa (Ref. 2). They successfully induced cancer by applying coal tar to the ears of rabbits and thereby produced the first experimental animal analogy of a type of chemically induced human cancer. The work of these Japanese investigators in 1915 was quickly followed by similar investigations in many laboratories and culminated in the isolation from coal tar of the carcinogenic polycyclic hydrocarbon benzo[a]pyrene by Kennaway and Cook (Ref. 3). But it was only in 1938 that Hueper experimentally produced bladder cancer in dogs by administration of β-naphthylamine (Ref. 4).

The known causes of human cancer include physical, chemical, and biological agents. According to Boyland (Ref. 5):

> Reasonable estimates are that not more than 5% of human cancer is due to viruses and less than 5% to radiations. Some 90% of cancer in man is therefore due to chemicals, but we do not know how much is due to endogenous carcinogens and how much to environmental factors. An expert committtee (WHO, 1965) has concluded that at least half of all cancer in man is due to environmental factors. It should therefore be possible to prevent a great deal of human cancer by finding and removing chemical carcinogens from the environment.

In 1960, Dr. G. B. Mider prepared for a committee of the United States Congress a summary of the current state of scientific knowledge about the causes of cancer (Ref. 6). Despite major subsequent advances in our understanding of the role of microsomal enzyme metabolism in the action of carcinogens, in molecular biology, in virology, in our knowledge of the immunological aspects of cancer, and in the development of in vitro models for carcinogenesis, the summary of the causes of cancer prepared by Dr. Mider more than a decade ago is still essentially correct:

(1) Although cancer can be caused by extraneous agents, not all members of the exposed population will develop cancer. Those who are most susceptible can be identified only by experience.

(2) Even a powerful carcinogen requires weeks or months to elicit cancer in mice or rats and probably requires years in man.

(3) No change need be recognizable in the organ or tissue destined to become cancerous before the cancer itself appears

(4) Experience in the laboratory does not predict unequivocally the reaction of humans to the same agent. On the other hand, those few chemical and physical agents known to produce cancer in man, with the possible exception of inorganic arsenical compounds, have elicited cancers in animals.

(5) No one at this time can tell how much or how little of a carcinogen would be required to produce cancer in any human being, or how long it would take the cancer to develop.

(6) The effect of certain chemical carcinogens can be markedly increased by other compounds with little or no carcinogenic power.

(7) The accumulated evidence suggests the irreversibility of the cancerous response once it has been initiated and further suggests a cumulative effect.

(8) The most potent carcinogens, by their very strength, are almost sure to be discovered clinically. It is assuredly the less potent carcinogens that seem most important in human cancer and provide the real problem for evaluation. A major objective of experimental carcinogenesis is, therefore, the bioassay for the presence of weak carcinogens.

(9) Chemical configuration alone cannot be used to predict the ability of a new compound to produce cancer.

(10) Possession (by a substance) of a biological effect, known to be associated with a particular type of cancer production, may be of importance in assessing potential carcinogenicity. Examples are: estrogenic activity, goitrogenic activity, production of liver cirrhosis.

The special attention given to the prevention of cancer is reflected in the Food Additives Amendment of 1958 and Color Additive Amendments of 1960. In principle, both laws recognize that all substances have a potential for harm and that, conversely, there are conditions under which most substances may be used safely. However, both laws also provide that under no conditions are cancer-producing substances to be considered safe. This Congressional expression of concern about cancer-producing agents indicates the need to know about the cancer-producing potential of food additives.

USE OF ANIMAL TESTS TO IDENTIFY RISKS TO HUMAN HEALTH

Testing for acute toxic effects in animals has long been and remains today the primary basis for evaluating the safety of food for humans. Now, however, scientists also test substances in animals to assess their long-term, or chronic effects, including their potential to cause cancer.

The first chronic animal studies were conducted in the late 19th century, after it was found that certain diseases were associated with lack of certain essential dietary constituents. For example, vitamin C deficiency, which leads to scurvy and niacin deficiency, which causes pellegra, were extensively studied in animals after scientists discoverd that these diseases could be mimicked in animals. After it became apparent that laboratory animals were useful in studying nutritional diseases, scientists quickly concluded that animal experience might also be useful in predicting the long-term effects in man of ingestion of small amounts of chemicals. In the early 1930's, FDA scientists initiated some of the first long-term, or lifetime chronic feeding studies on substances to which humans are exposed. These studies—on lead arsenate pesticides—led, in 1940, to the establishment of limitations on the use of lead arsenate.

Since these early days of toxicology, the use of tests in laboratory animals to predict the long-term chronic effects of chemicals in man has been accepted by virtually all scientists and is today used by every technologically advanced country in the world. In the United States, many Federal agencies in addition to FDA, such as the Environmental Protection Agency and the National Cancer Institute, rely on these animal tests to assess the safety of a variety of compounds. In 1954, the National Academy of Sciences/National Research Council (the Academy) published a report entitled "Principles and Procedures for Evaluating the Safety of Intentional Chemical Additives in Foods." This report updated pamphlets published in 1951 and 1952 on the safe use of chemicals in foods. The 1954 report and subsequent publications by the Academy describe the widely accepted approach of animal tests for evaluating the safety of chemicals added to foods. The World Health Organization has also espoused the use of animal tests to assess the safety of food ingredients.

The difficulty of identifying chemicals that may cause cancer has been considered may times in the last 15 years, and distinguished expert committees of the World Health Organization, Food and Agricutural Organization, National Academy of Sciences/National Research Council, and Department of Health, Education, and Welfare, as well as FDA, have published reports setting down principles and guildelines. Again the accepted test model is the chronic test in laboratory animals. As Berenblum (Ref. 8) has pointed out, our existing knowledge does not provide a basis for firm agreement on the optimal conditions for carcinogenicity testing, but merely allows the setting down of minimal requirements for animal tests for carcinogenicity. These minimum accepted requirements include: (1) more than one species of animal should be used to demonstrate lack of carcinogencity; (2) continuation of testing for the "practical" lifetime of the animals to establish a negative finding; (3) use of test doses close to the pharmacologically active range, several orders of magnitude above the actual use level; (4) maximization of numbers of animals on test, recognizing the practical limitations on population size; (5) use of routes of administration analogous to those by which humans will be exposed; and (6) whenever possible, commencing exposure during pregnancy and continuing exposure in the offspring for a lifetime. The three principal tests of saccharin on which the Commissioner is basing the accompanying proposals generally meet these basic criteria.

Even with the best test system, it must be recognized that a positive result only labels a substance as a suspect human carcinogen; at the same time, a negative result does not necessarily exclude the possibility that the substance is carcinogenic for man. Furthermore, it should be remembered that absolute demonstration of noncarcinogencity, even in the species tested, is impossible. As J. Cornfield has indicated:

> Expression of results as confidence limits rather than as a test of significance is to be preferred, since even when the lower confidence limit is below zero and no positive evidence exists, the upper limit may well be above zero, and this will serve as a constant reminder that failure to uncover positive evidence of carcinogenicity is not the same as a positive demonstration of noncarcinogenicity (Ref. 9).

Questions are frequently raised about the signficance of carcinogensis observed in animal experiments based on the belief that the high dosages to which animals are customarity exposed have no relevance in the assessment of human risk. Indeed, such questions have been raised about the findings in the WARF, FDA, and Canadian studies that saccharin causes bladder cancer. The Commissioner therefore believes that it is important to clarify this crucial issue.

It should be recognized that, general, only high dosages will produce tumors in animals under the experimental conditions that must customarily be employed. In setting up model experimental systems, scientists have no choice but to use relatively small numbers of animals in comparison to the human population likely to be exposed. In order to obtain meaningful, consistent, and reproducible results, studies must be designed to produce a significant number of cancers in the animals under test.

Even as low an incidence of cancer as 10 percent in a group of 100 experimental animals, which would approach the limit of reproducibility, would exceed any acceptable human risk. An incidence of 0.01 percent would represent 20,000 out of the total U.S. population of 200 million, and would certainly be considered unacceptably high. But to detect such a low incidence in experimental animals using dosage levels comparable to those administered to humans would require literally tens of thousands of animals. For this reason, scientists administer large doses to relatively small groups of experimental animals and then extrapolate the results to estimate the risk of cancer at low dosages.

Several methods for making such calculations of risk have been employed, but based on present knowledge and experience, the Commissioner believes the proper conservative approach is to assume a direct proportionality between the size of the dose and the incidence of tumors. For example, if a daily dosage of 1 gram per kilogram (kg) fed to experimental animals over a 2-year period produces a 10 percent incidence of tumors, FDA would assume that there would be a 1 percent incidence with 0.1 gram per kg dose, or a 0.1 percent incidence with a 0.01 gram per kg dose. Using this method of calculation, the agency would estimate, conservatively, that if a substance produces a 10 percent incidence of cancer in the rat at a dose of 1 gram per kg, it would produce a 0.01 percent incidence, representing 20,000 persons out of a total population of 200 million, if ingested by man at a dose of 1 milligram per kg.

It is important to recognize that such calculations may indicate only a minimal risk. Experimental assays are conducted under controlled dietary and environmental conditions with animals of homogeneous genetic background, while humans live under diverse conditions and are genetically heterogeneous, and are therefore likely to include subpopulations of unusual susceptibility.

Another popular misconception about the use of high dosages in animal carcinogenesis testing is the belief that any substance will induce cancer in animals if fed at sufficiently high levels. Excessively high levels of most substances can induce toxic effects in animals, but only a small number of such substances can produce cancer. This fact is illustrated by a study of 120 pesticides and industrial chemicals reported by J. R. M. Innes, et al. (Ref. 10). The compounds were selected on the basis of toxicity evidence suggesting potential harm to man, widespread use, or chemical structure suggesting possible carcinogenicity. In this study, both sexes of 2 hybrid strains of mice were orally administered maximum tolerated doses of the 120 test compounds starting at the age of 7 days. The authors found that administration of only 11 of the compounds unequivocally induced a significantly elevated incidence of tumors.

D. CARCINOGENICITY TESTING OF SACCHARIN

The first long-term study to evaluate the chronic toxicity of saccharin in the diet of rats was reported at FDA in 1951 by Fitzhugh, Nelson, and Frawley (Ref. 11). Various levels of saccharin were fed, some as high as 5 percent of the diet, to 10 male and 10 female rats per dosage level. At the conclusion of the study, the authors reported:

> No pathological effect whatever could be attributed to saccharin at levels of 1.0 percent or less. At 5 percent only one effect was noted, in the latter part of the experiment, namely an increased incidence of the ordinarily uncommon condition of abdominal lymphosarcoma. In the 5 percent group there were seven animals with lymphosarcomas; this number is not out of line with the incidence in comparable groups of rats, but the fact that in four of the seven rats abdominal as well as thoracic lymphosarcomas were present is unusual, since ordinarily the ratio is about 1 to 15–20. Three of these four combinations occurred in animals on experiment one hundred and two or more weeks.

In 1969, FDA pathologists reevaluated the findings from the Fitzhugh study (Ref.12). They concluded:

> The only effect of treatment during life was retardation of growth at 5 percent. In regard to pathological changes, our diagnoses of individual lesions were almost identical to those of Dr. Nelson. However, there were differences of opinion as to the role played by saccharin. Dr. Nelson stated in his 1951 report and also in the paper previously mentioned that the only pathological effect of saccharin was an increase in the incidence of the ordinary uncommon condition of abdominal lymphosarcoma. While we were not impressed by this, our examination of the written data and the microslides led us to conclude that saccharin had induced 2 lesions, and possibly a third. (1) Papillary excrescences from the papilla and papillocalyceal junction of the kidney in 13 of the 17 rats with kidneys sections microscopically

at 5 percent, 3/18 at 1 percent, and 1/15 at 0.5 percent. The papillary excrescences were the result of edema, vascular congestion, leukocytic infiltration, and fibroblastic proliferation of the stroma, stratification of the normally simple cuboidal epithelium to the stratified cuboidal or transitional type, calcium deposition, and in a few instances, phlebothrombosis. (2) Increased cellularity of the bone marrow at 5 percent. (3) While we have presented evidence which suggests that saccharin may have increased the incidence of the malignant lung tumor, lymphosarcoma, which occurs spontaneously in the rat and was very common in FDA rats at the time this study was performed, the data are inconclusive. A consideration of this, the presence of the renal changes, and the lack of knowledge as to whether the urinary bladder was affected strongly suggest the need for another two-year experiment.

A second long-term test of saccharin by oral administration to rats was completed in 1959 by Lessel (Ref. 13). As in the earlier Fitzhugh study, rats were fed saccharin for 24 months at levels up to 5 percent of their diet. Twenty male and 20 female rats were used per group. Lessel included a positive-control group to determine the susceptibility of his rats to the development of this tumor type, which he felt resembled the lymphosarcomas noted by Fitzhugh et al. Lessel found this type of tumor among the various tumors noted in both controls and treated animals; however, he did not find the incidence of tumors in the rats to be altered by the presence of saccharin in the diet even at the highest level (5 percent) fed.

In 1969, a re-study of the urinary bladders of some rats from the Lessel study was undertaken; however, all of the rats were not examined and the procedure used in the fixing of the urinary bladders would not be regarded as adequate by qualified experts. On gross observation of the rats, bladder abnormalities were noted at all feeding levels. Five males and three females at the 5-percent level exhibited these abnormalities. The author concluded that saccharin promoted the formation of bladder stones which in turn led to the bladder lesions (Ref. 14).

In 1970, at the request of FDA, the previously described studies and other data on the safety of saccharin were evaluated by NAS/NRC. At the conclusion of its review, the Academy made the following recommendations:

> Long-term studies designed according to present-day protocols and including adequate investigation of effects on reproduction should be completed in at least two species. In view of the concern about effects on the kidney and urinary bladder, special attention should be given to pathological examination of these organs.

Based on the data available in 1970, the Ad-Hoc Subcommittee on Nonnutritive Sweeteners of the NAS Committee on Food Protection accepted 1 percent as a "no-effect" level of saccharin in the diets of rats and mice (Ref. 15).

Between 1970 and 1975, additional lifetime chronic feeding studies of saccharin were conducted in which the compound was fed to laboratory animals either at a single- or multiple-dose level. These studies were carried out in a variety of laboratory animals including rats, mice, and hamsters. Two of these modern studies yielded notable and troubling results. In both of these studies, diets containing saccharin were fed to male and female rats from weaning. At the proper age, these rats were bred and their offspring carried to lifetime. Thus, these offspring were exposed to saccharin in their diets from the time of conception until death. These two studies were conducted by FDA and in the laboratories of the Wisconsin Alumni Research Foundation (WARF).

The FDA study fed doses of 0.01, 0.1, 1, 5, and 7.5 percent saccharin to the laboratory animals. There were 50 males and 50 females in each dose group and 100 control animals (animals not fed saccharin). The study was terminated when the number of survivors in a test group fell to 20 percent of the starting number. Serial sacrifices were performed at 14 and 18 months. Of the 23 males fed the saccharin diet at the 7.5-percent level which were examined, 7 developed bladder tumors. No tumors were found at lower saccharin levels, but 1 of 25 males examined fed the control diet developed a bladder tumor. Of the female rats, bladder tumors were found in 2 of 31 examined animals fed the 7.5-percent diet. None were found in the control females nor in female rats fed the 5-percent or lower levels of saccharin.

The WARF study followed essentially the same protocol as the FDA study, except there were 20 males and 20 females per group and the study was terminated at 100 weeks. In the WARF test, bladder tumors were found in 7 of 15 male rats fed the diet containing 5 percent saccharin. No bladder tumors were found in the female rats at any level of saccharin feeding.

In the FDA study, the rats fed the higher dose levels (5.0 and 7.5 percent) tended to grow less well than did controls or those fed lower levels of saccharin; a body-weight deficit of about 15 percent prevailed throughout the test period. All other measurements of well-being were normal, however, including survival and organ weight/body weight ratios. In the WARF test, the high level (5 percent) saccarin-fed rats lagged behind the other groups during the period of rapid growth, but as adults revealed no difference in body weight. Indeed, the control group was the lightest among the males on test, but the weight range among the various groups was remarkably narrow.

The high dietary sodium ($Na+$) level introduced by feeding high levels (5 to 7.5 percent) of sodium saccharin (about 11 percent $Na+$) was taken into account in the FDA study by adding an equivalent level of $Na+$ as Na_2CO_3 to the diet of a group of rats fed the basal (no saccharin) diet. However, no test was made of $Na+$-free saccharin as opposed to soluble saccharin. This is an important issue, since, for example, the metabolic disposition of saccharin may be altered by higher $Na+$ levels; the question is not accounted for by the Na_2CO_3 control, nor is it clear whether carbonate is an appropriate anion for this particular study.

As previously explained, the rationale of animal testing for possible carcinogenic hazards to man contemplates maximizing the sensitivity of the bioassay system, requiring administration of the highest tolerable dose along with appropriate lower doses. Because saccharin has a low toxicity, dose levels as high as 5 to 7.5 percent of the diet were fed in the FDA and WARF studies. As of 1974, tumors had been associated with saccharin feeding only at these high levels and in only two of many studies—those conducted by FDA and by WARF. This result raised uncertainty as to whether saccharin itself was the carcinogen, or whether the bladder tumors were induced by an impurity in the saccharin (orthotoluenesulfonamide) that was present at a detectable dose when high levels of saccharin were fed.

In addition, the high levels of saccharin fed were thought to raise the problem of calculus formation (Ref. 16). Calculi were associated with the occurrence of bladder tumors in the study by Hicks et al., (Ref. 17). Orthotoluenesulfonamide is a carbonic anhydrase inhibitor which can increase urinary pH, predisposing to calculus formation. Clayson found that bladder tumors due to certain sulfonamides were eliminated by feeding NH_4Cl to give an acid urine (Ref. 18). Furthermore, saccharin alone may cause bladder calculi (Ref. 19). This was thought to be potentially important, because there is evidence that bladder stones may play a determining role in the appearance of bladder tumors in the rats. Occurrence of bladder stones and increased urinary pH associated with saccharin feeding were not investigated in the FDA or in the WARF study. It was thought that this phenomenon may be critical in the embryo or newborn rat that is exposed to saccharin.

It should be emphasized that in both the FDA and WARF tests the offspring (F_1) generation of rats, i.e., those that were conceived after the parental generation had been placed on the saccharin-containing diets, were held and observed for manifestation of toxicity. The relatively high sensitivity of experimental animals to transplacental exposure to carcinogens has become obvious in recent years (Ref. 20). A number of carcinogens have been shown to be effective at very low levels by the transplacental route. Frequently, exposure of the pregnant female is associated with the relatively early appearance of tumors in the offspring. Despite these important implications, information about transplacental carcinogenesis is limited. For example, the dose level to which the fetus is exposed is often unknown, nor is there an understanding of the importance of developmental state, metabolic capacity, immune competency, and factors related to fetal pharmacology.

Even with these uncertainties, however, the F_0—F_1 feeding procedure is considered to be an appropriate and essential test because saccharin may be consumed by pregnant women as well as in-

dividuals of all ages. The technique of in utero exposure in lifetime testing has been recommended by an expert on carcinogenesis of the FDA Advisory Committee on Protocols for Safety Evaluation, J. Tox. and Appl. Pharmacol., 20:419–438 (1971). The panel recognized that exposure of an animal to a chemical early in life, even during pregnancy, may be important in influencing expression of carcinogenesis later in life. The panel stated that "since one of the important purposes of the chronic toxicity tests is the detection of carcinogenic potential, it would seem desirable to begin the exposure as early in life, i.e., as close to conception as possible."

The International Agency for Research on Cancer of the World Health Organization (IARC Scientific Publications No. 4) has also endorsed the need to consider in utero exposure in the study of carcinogenesis potential. The IARC report noted that "experimental studies have indicated the increased susceptibility of neonatal animals to the carcinogenic insult. The logical development of studying the effect on the rodent fetus of maternal exposure to a chemical carcinogen has made it clear that this pathway could well be operative in the human fetus."

Unfortunately, in neither the WARF study nor the FDA study were the rats in the parent (F_0) generation continued for long-term carcinogenicity testing of saccharin; thus no comparative data on the susceptibility of F_0 and F_1 rats in an internally controlled experiment were obtained. Therefore, at the conclusion of these studies, doubt remained about whether the concurrence of transplacental exposure and of bladder tumors was causally related.

Because of the continuing questions about the carcinogenicity of saccharin, in June 1972, FDA once more called upon the Academy to review the results of all experiments on the issue. To be able to provide FDA with a complete and up-to-date report, the Academy delayed completing its review until several studies, including the FDA study, then underway, were completed.

The Academy's report was received by FDA in December 1974. The report's primary conclusion was that the data then available had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." This conclusion was based in part on the uncertainty about the role of orthotoluenesulfonamide (OTS) in the induction of tumors. The Academy recommended that additional research on saccharin be conducted to determine whether saccharin is a carcinogen. The Academy recommended further that FDA reconsider the question when a substantial portion of the additional data became available.

E. CANADIAN STUDY

The recently reported Canadian study was initiated in February 1974 under the sponsorship of the Department of Health and Public Welfare of the Canadian Government (Toxicity and Carcinogenicity Study of Orthotoluenesulfonamide and Saccharin, Project E405/405E). Two generations of test animals (the F_0 and F_1 generations) were fed OTS and OTS-free saccharin to evaluate the toxicity and carcinogenicity of these compounds. The study on saccharin was the third experiment in which rats were exposed to saccharin during their period of development in the uterus and then throughout their entire life span. Both the earlier FDA and the WARF studies had shown an increased incidence of bladder tumors in male rats, but had left unresolved the question whether the tumors were caused by saccharin itself or by OTS. The Canadian study was designed to clarify this question by testing the OTS by itself as well as by testing purified saccharin containing only minimal amounts of the impurity. The Canadian study was thus designed to resolve the uncertainties noted by the NAS in its 1974 report.

Six groups of 50 male and 50 female rats were included in the study: a control group, 3 dose levels of OTS at 2.5, 25, and 250 milligrams per kilogram per day, a group receiving 5 percent saccharin (2,500 milligrams per kilogram per day) in the diet, and a group receiving 250 milligrams per kilogram OTS per/day and 1 percent ammonium chloride in the drinking water. The doses of OTS incorporated the amount of OTS, ranging from 0.6 to 27 miligrams per kilogram OTS per day, which may have been consumed by animals in the FDA and WARF studies on saccharin. OTS, a weak carbonic anhydrase inhibitor, may have a tendency to produce a slightly alkaline urine, possibly resulting in an increased incidence of bladder stones. Therefore, ammonium chloride was added to the drinking water of one OTS group to prevent this effect by producing a more acidic urine. The rats were observed daily, their weights and food consumption were recorded weekly, and 20 males of each generation of controls, saccharin treated, and high-level OTS treated animals with and without ammonium chloride had urine examined at 6-month intervals for microscopic calculi and parasite eggs.

The results of the Canadian study have been evaluated by expert pathologists, including scientists from FDA and other institutions in the United States, from Great Britain, and from other European countries, as well as from Canada. The findings indicate unequivocally that saccharin causes bladder tumors in the test animals. Specifically, 7 male and no female rats in the F_0 generation developed bladder tumors. Twelve male and two female rats in the F_1 generation developed bladder tumors. Thus, of a total of 200 rats fed saccharine, 21 developed bladder tumors.

In sharp contrast, of 100 control animals—those not fed saccharine or OTS—only 1 developed a tumor. Moreover, the low incidence of tumors in the animals fed OTS clearly resolves the earlier speculations, based on the FDA and WARF studies, that OTS and not saccharin may have been responsible for the cancers in the test animals. No evidence of bladder parasites was found in any of the rats. Microscopic crystals were found in the urine but the distribution did not seem to be related to treatment. Two grossly visible bladder stones were found in rats bearing tumors, one receiving saccharin and the other receiving OTS, while six were found in animals of various groups without bladder tumors. There was no significant increase in bladder tumors in any of the group treated with OTS.

F. ASSESSMENT OF HUMAN RISK

An important question raised about the animal studies on saccharin is their relevance to human beings. Public reaction to recent publicity about the Canadian study suggests considerable misunderstanding about the nature of toxicity testing in animals and the interpretation of results. For example, it has been widely publicized that the dose of saccharin found to be carcinogenic in rats is about 1,000 times that ingested by a human in a single diet beverage (when both doses are adjusted for the difference in body weight between rats and humans). Since this amount of saccharin would clearly never be ingested chronically by any person, some have suggested that these results have no pertinence whatsoever to human risk. In the judgment of FDA, this conclusion is not valid for the reasons to be described in this section.

Before dealing with the saccharin data specifically, however, the principles of appraising the risk of chemical carcinogenic substances should be explicitly stated. Those principles are as follows:

1. Certain substances can be shown in validly controlled animal experiments to increase the incidence of benign and/or malignant tumors. This result does not occur with all chemicals, only with certain ones.

2. Those substances that cause benign or malignant tumors in one species often also do so in other species. Therefore, any substance that causes such tumors in any species must be considered a potential carcinogen in man.

3. Chemical carcinogens, like other toxic substances, generally demonstrate a dose-response relationship, i.e., the the greater the dose the greater the tendency to produce tumors, and vice versa. The predominant opinion among experts in the field of carcinogenesis is that the dose-response principle extends to very low doses of the carcinogen—that is, that there is no dose, however small, at which one can be certain there is no risk. In other words, there is no threshold dose below which a carcinogen may be considered safe in the absolute sense.

4. Estimation of the risk of a low dose of a carcinogen in animals requires that one test the carcinogen at a dose high enough to produce tumors in the group of animals tested and then calculate what the risk is likely to be at a very small dose. The intent of animal testing is not only to identify potential risks such as carcinogenesis but also to estimate whether such an effect is likely to occur with a frequency, e.g., of 1 in 100, 1 in

1,000, 1 in 10,000, 1 in a 100,000, 1 in a million, etc. Since the actual measurement of a single event once in, e.g., 1,000 times, requires several thousand animals, it is evident that direct measurement of low frequency events cannot feasibly be done because of limitations on cost, the difficulty of handling large numbers of animals, etc. The problem is thus currently solved, albeit imperfectly and not without difference of opinion among experts, by conducting tests with a feasible number of animals at high doses and extropolating the results to low doses.

5. The method of extrapolation of results obtained at high doses to low doses should be a "conservative" method, i.e., it should err in the direction of overstating risk rather than understating it. Two accepted methods that meet this principle are the linear extrapolation method and the Mantel-Bryan procedure. In the dose range under consideration, the two methods give similar results for saccharin. The linear extrapolation method has been used in the FDA calculation on saccharin because it is easier to explain and understand.

6. The results of animal tests and their extrapolation to low doses provides an estimate of the risk of developing a tumor in the species tested. If one is to assume that such results are directly applicable to man, one must assume that one lifetime in the test animal is equal to a lifetime in man and that the test animal and humans are equally sensitive to the carcinogen. These assumptions are clearly open to debate, but in the absence of data to the contrary, the opinion of most experts is to assume that they are applicable. In the case of some carcinogens, wide variation among species in their sensitivity to the chemical has been demonstrated. The current view of experts is that these differences are due, at least in part, to species differences in the way the carcinogen is metabolized. In the case of saccharin, the drug is metabolized little, if at all, in either the rat or man. This fact supports the assumption that results from testing in rats are applicable to human risk assessment. The FDA risk estimates are then based on the principle that risk estimates in the rat are directly applicable to man.

Current scientific methods are not capable of determining the exact risk to humans of a chemical found to be carcinogenic in animals. However, techniques are available for estimating the upper limits of the risk. The Food and Drug Administration estimates that the lifetime ingestion of the amount of saccharin in one diet beverage per day results in a risk to the individual of somewhere between zero and 4 in 10,000 of developing a cancer of the bladder. If this risk is transposed to the population at large and if everyone in the United States drank one such beverage a day, this would result in anywhere between zero and 1,200 additional cases of bladder cancer per year. These estimates are identical to the estimates recently presented publicly by representatives of the Food and Drug Administration and of the National Cancer Institute (NCI) in hearings before the Health Subcommittee of the House Committee on Interstate and Foreign Commerce. The approach used in their calculation is described in the following paragraphs.

In the Canadian study, a 24 percent incidence of bladder tumors (12 of 50) was noted in the second generation male rats fed saccharin in a dose of 5 percent of the diet. This was the most sensitive group in the study to the carcinogenic effect of saccharin. Thus, in the absence of evidence that factors involved in its sensitivity are not relevant to the human population, this group is used to estimate the upper limit of human risk. There were no bladder tumors in an untreated control group of comparable size. Although the observed incidence of bladder tumors was 24 percent, the upper limit of risk in this study at the 95 percent confidence level is 36 percent. A 5 percent dietary level of saccharin in the rat is equivalent to 2,500 milligrams/kilogram/day of saccharin. If a 60-kilogram human (approximately 132 pounds) were to ingest 150 milligrams/day of saccharin (i.e., 2.5 milligrams/kilogram/day over a lifetime, he or she would thus receive the equivalent of one one-thousandth of the rat dose per day. This dose is approximately that contained in one large diet beverage drink (12½ ounces) per day.

Since rats fed 2,500 milligrams/kilogram/day may have as high as a 36 percent incidence of bladder tumors, ingestion by rats of one one-thousandth of that dose could yield, by linear extrapolation, an incidence of 0.036 percent or 4 cases per 10,000.

The lifetime risk of bladder cancer in humans in the United States is 1.5 percent; that is, of every 10,000 persons, it is expected that 150 will develop bladder cancer sometime during their lives. Extrapolating from the Canadian rat study, and if one assumes a direct correlation between the estimate of maximum risk of saccharin in rats and in humans, if a human ingests 150 milligrams/day of saccharin for a lifetime, he could increase the risk of bladder cancer by 0.036 percent, for a total risk of approximately 1.54 percent. That is, of every 10,000 persons, 154 might develop bladder cancer (if they all use 150 milligrams/day of saccharin) and if the assumptions are valid.

The risk from use of 150 milligrams/day of saccharin over a lifetime can be assessed in another fashion. The annual case rate of bladder cancer in the United States is given by the NCI as approximately 30,000. If everyone in the United States ingested 150 milligrams of saccharin per day (e.g., from one large diet drink) over a lifetime, and if the other assumptions are correct, there could be approximately an additional 1,200 cases per year (or an increase in risk of 4 percent over the basal risk). If only half the population ingested 150 milligrams of saccharin per day over a lifetime, an additional 600 cases per year could occur (or an increase in risk of 2 percent over the basal risk).

The estimated increase risk from this moderate use of saccharin cannot be detected in human epidemiological studies. Such studies usually can only detect increased risks of 200 to 300 percent (i.e., 2 to 3 times the baseline rate) or greater. Even the best feasible epidemiologic study is not likely to detect an increased risk of only 2 to 4 percent over background incidence. Thus, for example, the author of one epidemiological study of bladder cancer in consumers of artificial sweeteners (Kessler, I. I., J. Urology, 115:143–146, 1976) noted that "The sample sizes used here would permit the detection of an 80 percent increase in bladder cancer owning to nonnutritive sweetener use * * *." This study would not, then, have detected any increase in bladder cancer due to saccharin consumption if the risk is at the level suggested by the Canadian study in rats.

As discussed previously, cancer has a long latent period, requiring 5 to 30 years before it can be detected. Although saccharin has been used in food for over 70 years, it is only in the past 15 to 20 years that its use has become substantial. Thus, it is probably too early to ascertain from human epidemiological studies the number of bladder cancers associated with saccharin consumption. This conclusion was reached by the authors of one of the epidemiological studies on saccharin (Armstrong, B. and R. Doll, Brit. J. Prev. Soc. Med., 28:233–40, 1974) who pointed out that "If the minimum time necessary to see a significant number of bladder cancers induced by saccharin were more than thirty years * * * it would be too early to see an effect of saccharin consumption on mortality rates."

In a third epidemiological study on saccharin consumption (Armstrong, B. et al., Brit. J. Prev. Soc. Med., 30:151–157, 1976) only about 600 of the diabetics studied had consumed saccharin for more than 25 years. This number is far too low to detect the level of risk from saccharin consumption suggested by the experiments in rats. The fact that these epidemiological studies in patients with diabetes who used saccharin for prolonged periods revealed no detectable increased in bladder cancer is therefore compatible with the available animal data. A common feature of all three epidemiological studies is their comparative insensitivity, which could permit a sharply increased incidence of bladder cancer attributable to consumption of saccharin—on the order of more than 20,000 cases per year in the American population—to go undetected.

By contrast, the risk of lung cancer from cigarette smoking (which FDA has no authority to regulate) is now readily detectable in human epidemiological studies. However, even though cigarette smokers have been shown to incur a risk of developing lung cancer that is 500 to 2,000 percent greater than the risk of lung cancer incurred by nonsmokers, depending on how much they smoke, it

took many years to recognize and document the increased risk. The first suggestions of an association between cigarette smoking and lung cancer were not made util the late 1930's (Muller, F. H., Z. Krebsforsch, 49:57–84, 1939). Several epidemiological studies reported an association between cigarette smoking and lung cancer in the early 1950's, but widespread acceptance of the relationship did not occur until publication of the 1964 report to the Surgeon General entitled Smoking and Health.

The Food and Drug Administration thus considers the animal data and the human epidemiological data on saccharin to be compatible. The estimated excess risk to the individual of developing bladder cancer from lifetime use of, e.g., 150 milligrams of saccharin per day, is believed to be somewhere between zero and 4 per 10,000. The estimated population risk in the United States, assuming such use by each individual, is somewhere between zero and 1,200 cases per year.

Although the risk from consumption of saccharin is small compared to that of other health hazards, e.g., cigarette smoking, saccharin is only one of a potentially large number of hazards present in our environment. The Commissioner believes that reduction of prolonged, general exposure to a number of weakly carcinogenic substances in our environment as they are discovered may be essential to reduce the total incidence of cancer.

G. LEGAL BASIS FOR ACTION

Press reports of the announcement of FDA's intention to withdraw approval of saccharin as an ingredient in foods and beverages have given the impression that the Commissioner is acting reluctantly, based exclusively on the Delaney anticancer clause of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348 (c)(3)(A)) and, further, that the agency's action was triggered solely by the findings of the Canadian study. Neither impression is accurate.

As should be clear from the foregoing discussion, questions about the safety of saccharin have persisted almost from the date of its introduction. Serious doubt about its potential for causing cancer in laboratory animals arose much later, but this concern, too, is not new. Before the Canadian study, two scientifically sound and generally well-conducted studies had suggested an association between saccharin and bladder cancer in animals exposed to high doses of the sweetener. The Canadian study unequivocally confirms this association and lays to rest speculation that the causative agent may have been OTS. There can no longer be any doubt that saccharin causes a sharply increased incidence of bladder cancer in test animals.

The discussion in the previous section makes clear that the human risk of cancer indicated by these findings is significant and cannot be ignored. The Commissioner believes that conscientious protection of the public health is not consistent with continued general use in foods of a compound shown to present the kind of risk of cancer that has been demonstrated for saccharin—regardless of the asserted benefits of its use for some individuals in the population.

Section 409(c) of the act (21 U.S.C. 348(c)) requires that any food additive must be found to be safe for human consumption before it can be approved or, in case of an additive already approved, continue to be used in foods. Based on the accumulated evidence of hazard associated with ingestion of saccharin, culminated by the Canadian study, the Commissioner concludes that the finding required by the statute can no longer be made, and that the interim food additive regulation approving the use of saccharin should be repealed.

FDA has previously prohibited the use in food of ingredients found to cause cancer in laboratory animals to which the Delaney clause was not applicable. For example, in January 1950, before enactment of the Delaney clause, FDA prohibited the use in food of two artificial sweeteners as "poisonous substances." This conclusion was based in large part on the finding of liver tumors in rat studies. In May 1968, FDA prohibited the use in food of the flavoring agent, oil of calamus, based on a finding of carcinogenicity in animal studies. Oil of calamus had been used in food on the determination that it was generally recognized as safe; thus, the Delaney clause did not apply. There are a number of other examples. In short, although FDA has acted on a number of occasions to remove carcinogenic substances from the food supply during the past 25 years, only two previous actions—both involving minor indirect food additives—have been based on the Delaney clause.

Those actions, like this one, were based on certain well-recognized postulates about chemical carcinogenesis: (1) there is reason to believe that those substances which cause cancer in animals may also cause cancer in man; (2) animal tests, despite inadequacies, provide the best evidence currently available about the potential of chemicals to cause cancer in humans; (3) there is no reliable basis for concluding that there is a completely "safe" level of a carcinogen, i.e., a threshold level that will not cause cancer in some members of the population; and (4) cancer appears to be an irreversible process, in both test animals and in man.

It is of course true that the present law would afford the Commissioner no choice but to prohibit the marketing of saccharin as an ingredient in foods even if he were not persuaded that the scientific evidence independently warranted such action. The Delaney anticancer clause specifies that "[N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." (21 U.S.C. 348 (c)(3)(A).) There can no longer be any question that saccharin does cause cancer when ingested by laboratory animals, in this instance in tests that the Commissioner would in any event regard as appropriate for the evaluation of carcinogenicity.

Therefore, under both the general safety requirement of the Food Additives Amendment of 1958 and the Delaney anticancer clause, the Commissioner concludes that saccharin may no longer be approved as a food additive. This proposal is issued to comply with the procedural requirements of section 409(h) of the act. The Commissioner welcomes comments on any facet of this proposal, including the reasonableness of his judgment about the safety of saccharin under the law. He feels constrained to point out, however, that the wisdom of the Delaney clause is not at issue in this proceeding. FDA could not ignore that provision even if the Commissioner were persuaded that the risks to human health were less than they appear. He further notes that under the provisions of the law relating to food additives, FDA is not empowered to take into account the asserted benefits of any food additive in applying the basic safety standard of the act.

The Commissioner does recognize, however, the potential medical value of permitting saccharin to remain available for individuals who may depend on a nonnutritive sweetener to maintain a diet free from sugar, provided such products can meet the standards of the drug provisions of the act. This subject is addressed in the following part of this preamble, on which the Commissioner specifically invites comments from specialists in the treatment of diabetes and obesity.

II. USE OF SACCHARIN IN DRUGS

A. HISTORY OF DRUG USE OF SACCHARIN

In addition to being used in foods, saccharin has been used in drugs for a number of years as a sweetening agent to improve the taste of oral drug products. Thus saccharin is used extensively in such drugs as pediatric liquid preparations, chewable tablets, and mouthwashes and toothpastes with drug claims. When used as a sweetener in a drug product, it is usually used in conjunction with a nutritive carbohydrate sweetener, such as sucrose or sorbitol, to mask the bitter aftertaste often experienced with saccharin. Saccharin is a pharmaceutical aid in liquid pediatric products where palatability is important to induce small children to take the medication. The volume of sucrose needed to provide acceptable levels of sweetness in some of these products has posed problems of incompatibility in the formulation in certain products.

The quantity of saccharin used as a flavoring agent in drug products covers a wide range. For example, of 12 penicillin V potassium products for oral suspension that were examined, the concentration of saccharin ranged from a low of 5.2 milligrams per teaspoonful to a high of 42.8 milligrams per teaspoonful. If a pediatric liquid oral preparation contains 40 milligrams of saccharin per teaspoonful (one dose) and the maxi-

mum daily dose is 2 teaspoonfuls four times a day, a child could consume 320 milligrams per day of saccharin from this one drug. Obviously, if other products containing saccharin were also being consumed, the daily intake of saccharin would be much higher. It should also be noted that drug products can be used for both the treatment of acute and chronic conditions. Thus, if a drug product containing saccharin is administered daily for the treatment or prophylaxis of a chronic condition, such as rheumatic fever, the patient could be exposed to a daily amount of saccharin equivalent to that contained in one or more diet soft drinks.

Saccharin is also marketed in tablet, powder, and liquid forms as a so-called "tabletop sweetener" for use in conditions in which nutritive carbohydrate sweeteners in the diet must be avoided. Certain of these products meet the statutory definition of a drug in that they are recognized by the U.S. Pharmacopoeia or the National Formulary. In addition, they have at one time or another been tacitly recognized by FDA as drugs. In recent years, however, such products have been marketed and regulated as food additives.

In light of the recent Canadian study's unequivocal demonstration that saccharin causes malignant bladder tumors in test animals, the Commissioner has examined the use of saccharin in drug products, both as an inactive ingredient and as an active ingredient. In his judgment, the safety considerations involving the use of saccharin in drug products differ from those regarding its use in foods. Moreover, the Delaney clause does not apply to drug products. An ingredient that is clearly unjustified for general use in foods for humans may be suitable for use as a drug when there is a legitimate medical need that outweighs the risks of possible adverse effects. The Commissioner is thus permitted under the drug provisions of the law to evaluate the risk of using saccharin compared to the benefits of its use as a drug ingredient.

B. Saccharin As An Inactive Ingredient in Drug Products

With respect to the use of saccharin as a pharmaceutical aid, the Commissioner has tentatively concluded that the risk of such use in most drug products is not outweighed by the benefits, and thus, saccharin will not be permitted as an inactive ingredient unless it affords an overriding benefit. The Commissioner therefore proposes to add new § 310.514 to Part 310 (21 CFR Part 310) of the new drug regulations, declaring that any drug product for human use containing saccharin as an inactive ingredient is a new drug and is misbranded unless such product is specifically exempted from the regulation. The Commissioner bases this proposal on the fact that the use of saccharin in most drug products as an inactive ingredient produces no direct therapeutic benefit. Thus, the possible risk associated with the use of saccharin for such purpose is medically unjustified. This is particularly true because individuals do not have the opportunity to choose whether or not to take such a risk if saccharin were to remain available as an inactive ingredient in drug products.

In § 310.514, the Commissioner proposes that any holder of an approved new drug application for a drug product containing saccharin as an inactive ingredient be required to submit to FDA within 9 months of the date of publication of the final regulation, a supplemental application providing for a new revised formulation removing saccharin as an ingredient. The revised formulation may not be marketed before the receipt of written notice of approval of the supplemental application by FDA. Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing saccharin as an ingredient shall amend the IND notice within 9 months of the date of publication of the final regulation to revise the formulation removing saccharin as an ingredient. Under the proposal, the Commissioner would initiate action to withdraw approval of an application or terminate an IND notice if any current holder of an approved new drug application or sponsor of an IND notice fails to submit a supplemental application or to amend an IND notice as set forth, and within the time periods provided for, in § 310.514.

A period of 9 months for the submission of supplemental applications is being proposed to allow manufacturers time to reformulate their products and perform the stability and bioavailability studies, where necessary. Depending upon the type of product, i.e., tablet or liquid, and the amount of saccharin currently in the product, reformulation to maintain palatability may pose problems. For example, attempts to raise the content of nutritive sweeteners to mask the bitter taste of a drug is limited by such physical factors as solubility. Further, because of the increased nutritive sweetener content, a preservative may have to be added. Likewise, as of July 7, 1977, firms, will also have to comply with the bioavailability requirements as set forth in §§ 320.21 and 320.22 (21 CFR 320.21 and 320.22) of the regulations. Similar provisions, applicable to antibiotic drug products, are set forth in a new § 430.300 that the Commissioner proposes to add to Part 430 (21 CFR Part 430) of the regulations.

Because of the potential need for specially formulated drugs for diabetics or for special situations in which saccharin may be necessary for the product as a pharmaceutical aid, the Commissioner is also proposing a specific provision under which a petition may be submitted to FDA requesting that a specific use of saccharin as an inactive ingredient be permitted. To support such a petition, the person requesting the exemption must submit the following information: (1) the amount of saccharin in the drug product; (2) is saccharin is included as a pharmaceutical aid, an adequate showing that there are no technically feasible alternatives to saccharin, or an adequate showing that the drug product containing saccharin provides a substantial health benefit that would not be available without the use of saccharin, for example, the product is one specifically formulated for diabetics; and (3) copies of the proposed labeling specifying the saccharin content.

Whether or not the drug product is subject to the requirements for an approved new drug application or for antibiotic certification, under the proposal, a drug product containing saccharin as an inactive ingredient shall, unless exempted, not be manufactured after 15 months and shall not be initially shipped into interstate commerce 18 months from the date the final regulations are published in the Federal Register. Initial introduction into interstate commerce of a drug product for purposes of this regulation means the first shipment of the final dosage form of the drug product into interstate commerce pursuant to a sale or consignment to an independent party. Since these dates are applicable to all drug products, firms submitting supplemental new drug applications or amendments to antibiotic drug files should assure that they are complete when they are submitted.

C. Saccharin As A Single-Active-Ingredient Drug

Saccharin has been available for many years in single-active-ingredient products for use by individuals who must control their caloric intake. These products consist of tablets, liquids, or powders containing saccharin as the primary sweetening ingredient, and some are popularly known as "tabletop sweeteners." For the most part, these products have been regulated by the agency as food additives, and most recently as special dietary foods (see 21 CFR 105.79, formerly 21 CFR 125.7 prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)).

These products have also historically been recognized as drugs. The Referee Board of the United State Department of Agriculture, while considering the safety of saccharin in foods in 1912, stated, "The Food and Drug Act provides that any substance which is intended to be used for the prevention, cure, or mitigation of disease is a drug, and a product containing saccharin and plainly labeled to show that the mixture is intended for the use of those persons who, on account of disease, must abstain from the use of sugar, falls within the class of drugs * * *." This statement by a board of scientific advisors indicates that, even as early as 1912, saccharin was recognized as a drug when offered for sale for use by persons with a medical need to limit nutritive sweeteners in their diets.

The United States Pharmacopoeia has recognized saccharin as a pharmaceutical aid since at least 1926. The current edition of the National Formulary recognizes saccharin calcium, saccharin sodium, and saccharin sodium tablets. By

virtue of the recognition of those products in the official compendia, and depending on their labeling, they may fall within the definition of "drug" in section 201(g) of the act (21 U.S.C. 321(g)).

Saccharin was reviewed in the mid-1950's under the new drug provisions of the act as an active ingredient of a new drug product in combination with a cyclamate salt, but the new drug application for this product is no longer approved. In addition, as recently as August 27, 1975 (40 FR 38179), FDA published an amended notice requesting data and information on saccharin for review by its OTC Miscellaneous Internal Products Panel. This publication was a part of the agency's ongoing review of OTC drug products for human use currently marketed in the United States. Saccharin was included in the listing of ingredients under the product categories of sweeteners and weight control products. The Commissioner notes, however, that in response to the August 27, 1975 notice, no submissions of any type were made for any product containing saccharin as an active ingredient. The Bureau of Drugs of FDA thus has no request before it at the present time from any manufacturer to market saccharin either OTC or by prescription, under the OTC review or as a new drug.

Although single-ingredient tabletop sweeteners containing saccharin in the form of tablets, liquids, or powders have been subject to regulation as foods, the Commissioner believes that such products may be considered as drugs, depending upon the claims made for them. The essential criterion for determining whether a product is a drug is whether it meets the definition in section 201(g)(1)(B) and (C) of the act, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease in man or other animals," and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

Once determined to be a drug, a product must meet the standards of the drug provisions of the act, among them the safety and effectiveness requirements of either section 201(p) or 505. Section 201(p) states that a drug is a new drug if it is "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." If a new drug, the law requires among other things "substantial evidence that [it] will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof" (21 U.S.C. 355(d)(5)). Such substantial evidence means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (21 U.S.C. 355(d)(6)).

Finally, if a drug is otherwise marketable, the Commissioner must determine whether it should be considered as a prescription or OTC drug. The applicable standard (21 U.S.C. 353(b)(1)(B)) requires that a drug must be dispensed by prescription if, "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug."

The Commissioner recognizes that saccharin is the only product available on the market for use as a nonnutritive sweetener and that such use may be important to the proper dietary management of individuals who must control their intake of nutritive sweeteners. These include individuals with conditions such as diabetes, obesity, reactive hypoglycemia, and carbohydrate-induced hyperlipemia. Whether such use is properly construed as a drug use under the law depends upon the claims made by the manufacturer and is reasonably open to debate. The Commissioner is prepared to consider the possibility that such single-ingredient sweeteners may be marketable as drugs, even if the same formula might not be approvable as a food additive. The Commissioner believes, however, that the proper context for considering such a use under the drug laws is in reviewing new drug applications for individual products.

In reaching this tentative conclusion, the Commissioner has specifically excluded the possibility of reviewing the matter further as part of the OTC review. This review is fundamentally intended to identify those conditions under which specific ingredients can be generally recognized as safe and effective for OTC use within the meaning of section 201(p) of the act. There is no realistic prospect, however, that such a determination can be made for saccharin as a drug. Saccharin has no history of marketing in the United States as a drug approved for effectiveness under the Drug Amendments of 1962; general recognition of effectiveness under these conditions would seem to be precluded, even though effectiveness vel non may be demonstrated. Similarly, the Canadian study represents new evidence reflecting on the safety of the product which the Commissioner considers sufficient to remove it from the market as an approved food additive. In the face of this new evidence, general recognition of safety does not appear to be a reasonable possibility. For these reasons, the Commissioner concludes that saccharin is not a suitable ingredient for review by the Miscellaneous Internal Products Panel of the OTC Review, and the call of August 27, 1975 for submission of information on sweeteners to this panel is hereby rescinded.

The Commissioner believes that the new drug application is a more appropriate mechanism for considering the issues related to the marketability of saccharin-containing sweeteners for use by individuals who for medical reasons must limit their intake of nutritive sweeteners. He therefore invites comment on a proposal to add a new § 310.514(b) to the regulations which would permit the submission of new drug applications for such products. This authorization would be limited to consideration of tabletop sweeteners in packaging appropriate for use by individual patients. The agency will not entertain under this proposal new drug applications for any products that are clearly foods sweetened with saccharin, e.g., diet soft drinks, canned fruits, etc.

The proposed regulation requires that any manufacturer wishing to ship a single-active-ingredient sweetener containing saccharin in interstate commerce would have to meet the following conditions after publication of the final regulations:

1. Within 180 days, submit a new drug application for the product, meeting the requirements of § 314.1 of the regulations.

2. Within 120 days, label the product with the following interim indications statement: "For use as a noncaloric sweetener when a sugar-restricted diet is medically indicated, as in patients with diabetes" and with a warning statement concerning the risk of cancer. The Commissioner proposes the following warning statement, and solicits additional suggestions: "Warning: Saccharin causes bladder cancer in animals. Use of saccharin may increase your risk of cancer."

Any manufacturer not meeting these conditions would be subject to regulatory action.

The Commissioner proposes that those manufacturers whose products meet the requirements of this section will be permitted to market their products while their new drug applications are under review. Such marketing is permitted for a marketed drug which is newly declared as a new drug provided the Commissioner determines it is or may be medically necessary (*Hoffman-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975)). The Commissioner has determined that the continued marketing of saccharin as a single-ingredient drug meets this criterion, at least for purposes of permitting further consideration of the data and information in new drug applications, since saccharin is the only remaining sweetener on the market for patients on sugar-restricted diets.

The foregoing determinations should in no way be construed as committing the Commissioner to approve any new drug applications submitted either for the interim indication proposed or any other indication. Approval will depend on whether the products as labeled meet the definition of a drug and whether the evidence presented in these applications meets the criteria for approval set forth in the statute and in the regulations.

The Commissioner tentatively concludes that, if saccharin-containing sweeteners are labeled as drugs and if they are deemed to be otherwise approvable under the new drug provisions of the act, they may be marketed OTC. This conclusion is based on the lack of toxicity (other than risk of cancer, for which it will be labeled), the lack of other collateral measures necessary for its safe use, which would require a prescription, and the long history of safe OTC use of the product without a physician's prescription. The Commissioner invites comments on this tentative conclusion.

III. Use of Saccharin as a Cosmetic Ingredient

Saccharin is currently used as an ingredient in a number of cosmetic products, principally to affect taste. Many of these products, such as dentifrices (toothpastes) and mouthwashes, as well as lipsticks, are likely to be ingested under normal conditions of use. Although the risk of exposure to significant amounts of saccharin from any of these products may not be large, the use of saccharin affords no benefit sufficient to warrant the acceptance of any increased risk. The Commissioner therefore proposes to determine that the use of saccharin in any cosmetic product that is likely to be ingested and which is manufactured more than 30 days after the date of publication of a final regulation will result in the product being deemed to be adulterated under section 601(a) of the act (21 U.S.C. 361(a)).

IV. Use of Saccharin in Standardized Foods

Saccharin is listed as a mandatory ingredient in nine standards of identity for artificially sweetened fruit products. In addition two standards, 21 CFR 146.111 and 146.121 (formerly 21 CFR 27.128 and 27.103, prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)) list as a mandatory ingredient "one or more of the artificial sweetening ingredients listed in and complying with Parts 170 through 129 of this chapter."

The Commissioner proposes to amend those standards of identity for artificially sweetened fruit products that require saccharin to be used as the artificial sweetener by deleting the reference to saccharin and replacing it with more general language requiring the use of "one or more of the artificial sweeteners listed in and complying with Parts 170 and 189" of Chapter I of Title 21 of the Code of Federal Regulations.

When the ban on saccharin as a food additive takes effect, the marketing of the foods covered by the 11 standards will be unlawful. The Commissioner has opted to amend the standards rather than revoke them to conserve agency resources.

If the standards were revoked and an artificial sweetener was subsequently approved for use by FDA, the process of establishing standards for artificially sweetened fruit products would have to begin anew. By keeping the standards on the books, the Commissioner will avoid unnecessarily expending scarce agency resources. The Commissioner emphasizes, however, that his election of the amendment approach rather than revocation should not be taken to be an implied prediction that FDA will soon approve another artificial sweetener as a replacement for saccharin. The amendments are being proposed as a matter of administrative convenience, not as a harbinger of future approval of any artificial sweetener.

V. Use of Saccharin in Animal Drugs and Animal Feed

The use of saccharin as an ingredient in animal drugs or animal feed for food-producing animals requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act (sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B)) if it is a carcinogen, or by an assay designated under sections 409(b)(2)(D), 512(b)(7), and 706(b)(5)(A)(iv), in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist. Accordingly, the Commissioner proposes to ban saccharin for all uses in food-producing animals.

Since saccharin is also an ingredient in some animal drugs and feeds intended for use in non-food-producing animals, the Commissioner proposes to disapprove this use as well. Saccharin provides no therapeutic benefit to animals and has not been shown to provide any overriding benefit to a measurable animal treatment population. For these reasons, the Commissioner concludes that any risks to animals from the use of saccharin in such drugs outweigh any theoretical benefit alleged from its continued use.

VI. Compliance Policy

An important aspect of this proposal is, quite obviously, the compliance policy that FDA intends to adopt as part of the final regulations on saccharin. Matters of interest to consumers and manufacturers and users of saccharin alike are: When will the ban take effect? Will it apply to manufacture or shipment of saccharin containing foods? Is a recall contemplated? When must new drug applications be submitted? This section summarizes FDA's intended compliance policy when final regulations are issued.

A. Saccharin Used in Food

Under section 409(e) of the act (21 U.S.C. 348(e)), the final regulation revoking the interim food additive regulation for saccharin (21 CFR 180.37) shall be effective on publication in the Federal Register. The Commissioner intends, in the final regulation, to prohibit the addition of saccharin to any food (e.g., soft drinks) after the effective date of the final regulation. Foods that have been fully processed and packaged for sale to consumer or institutions on the effective date of the final regulation would be permitted to be sold. The addition of saccharin in the manufacture of food, further processing, or repacking, after the effective date of the final regulation will cause such products to be adulterated within the meaning of the act and subject to regulatory action.

B. Saccharin Used in Human Drugs

When a final regulation is issued, holders of approved new drug applications for a drug product containing saccharin as an inactive ingredient and sponsors of IND notices for a drug product containing saccharin as an ingredient will have 9 months to file a supplemental application (NDA) or amendment (IND notice) to revise the formulation removing saccharin an an ingredient. Similar requirements are proposed for antibiotic drug products.

Petitions may be submitted to FDA requesting that a specific use of saccharin as an inactive ingredient be permitted. Such a petition must include the information specified in section II.B. of this preamble.

Manufacture of any drug products containing saccharin as an inactive ingredient would be prohibited after 15 months from the date of publication of final regulations in the Federal Register Initial shipment of drug products containing saccharin as an inactive ingredient would be prohibited 18 months after the date of publication of final regulation in the Federal Register.

This proposal invites comment on the appropriateness of permitting the marketing of saccharin as a single-ingredient drug for use by persons who must restrict their intake of sugar, available without a physician's prescription. If the final regulation should permit such marketing, any manufacturer wishing to ship in interstate commerce a saccharin-containing tabletop sweetener would, within 180 days after the date of publication of the final regulation, have to submit a new drug application for the product and comply with the other requirements set forth in proposed § 310.514.

Tabletop sweeteners currently being marketed would be permitted to continue to be marketed as over-the-counter drugs, pending review and action on the new drug applications. The Commissioner cautions against substantial changes in the packaging format of saccharin as a single-ingredient product during this period. Within 120 days after publication of the final regulation, however, those products would have to be labeled with the statements prescribed in § 310.514(b)(2).

C. Saccharin Used in Cosmetics

A final regulation prohibiting the use of saccharin in cosmetics that are likely to be ingested will be effective 30 days after publication of a final regulation in the Federal Register. The addition of saccharin to cosmetics that are likely to be ingested after the effective date of a final regulation would be prohibited. Cosmetics containing saccharin that are already on the market and those prod-

ucts that are fully processed and packaged for sale to consumers or institutions before the final regulation takes effect will be permitted to be sold. The prohibition on saccharin in cosmetics does not apply to products that are not likely to be ingested (e.g., hair tonics).

D. SACCHARIN USED IN ANIMAL DRUGS AND FEED

The final regulation prohibiting the use of saccharin in animal feed will be effective on publication in the FEDERAL REGISTER. The Commissioner intends, in the final regulation, to prohibit the addition of saccharin to any animal feed after the effective date of the regulation.

The final regulation prohibiting the use of saccharin in animal drugs will be effective 30 days after publication in the FEDERAL REGISTER. After the effective date, it will be unlawful to manufacture an animal drug containing saccharin. Holders of approved new animal drug applications for products that contain saccharin as an inactive ingredient will be required to file a supplemental application within 9 months of publication of final regulations.

E. RECALL OF SACCHARIN-CONTAINING PRODUCTS

The Commissioner has concluded that the protection of the public health does not require the recall from the market of food, drugs (human and animal), animal feed, and cosmetics that contain saccharin or the destruction of products that are fully processed and packaged for sale to consumers or institutions when a final regulation is issued. Thus, at this time, no recall is contemplated and products that contain saccharin on the market or fully processed and packaged for sale to consumers or institutions when a final regulation is issued would be permitted to be sold.

As discussed earlier in this preamble, the Commissioner believes that prolonged consumption of saccharin in ordinary foods, such as soft drinks, and exposure to saccharin from other products (i.e., drugs, animal drugs and feed, and cosmetics) poses a significant risk of cancer and should not be permitted in the future. However, the potential risk of human cancer from saccharin is cumulative; though significant, it is not immediate in the sense that the exposure of consumers to saccharin must be halted at once. The relatively short period of time in which products containing saccharin already on the market will be sold, does not, in the Commissioner's judgment, significantly threaten the public health.

The Commissioner emphasizes, however, that there is a significant potential risk of cancer from prolonged consumption of saccharin. His judgment is that a recall—with all the attendant costs to the industry and consumers—is not required to protect the public health; but this judgment should not be construed as reflecting a lack of concern about the cumulative risk associated with the routine consumption of saccharin by the general population.

All FDA regulations concerning human food were reorganized under Subchapter B—Food for Human Consumption, published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302). For the convenience of the reader, the following table lists the former designation of the sections in recodified Subchapter B which would be amended by this proposal.

New section:	*Old section*
145.116	27.14
145.126	27.84
145.131	27.73
145.136	27.43
145.171	27.6
145.176	27.24
145.181	27.57
146.111	27.128
146.121	27.103
150.141	29.4
150.161	29.5
172.135	121.1056
172.820	121.1185
180.37	121.4001
189.185	121.106(d)

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

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Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 301, 401, 402, 409, 502, 505, 512, 601(a), 701 (a) and (e), 52 Stat. 1042–1043 as amended, 1046–1047 as amended, 1050–1055 as amended, 70 Stat. 919, 72 Stat. 1784–1788 as amended, 82 Stat. 343–351 (21 U.S.C. 321(s), 331, 341, 342, 348, 352, 355, 360b, 361(a), 371 (a) and (e))) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 145—CANNED FRUITS

1. In Part 145:

a. By revising § 145.116(a) to read as follows:

§ 145.116 Artificially sweetened canned apricots.

(a) Artificially sweetened canned apricots is the food which conforms to the definition and standard of identity prescribed for canned apricots by § 145.115(a), except that in lieu of a packing medium specified in § 145.115(a)(3), the packing medium

used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

b. By revising § 145.126(a) to read as follows:

§ 145.126 Artificially sweetened canned cherries.

(a) Artificially sweetened canned cherries is the food which conforms to the definition and standard of identity prescribed for canned cherries by § 145.125(a), except that in lieu of a packing medium specified in § 145.125(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

c. By revising § 145.131(a) to read as follows:

§ 145.131 Artificially sweetened canned figs.

(a) Artificially sweetened canned figs is the food which conforms to the definition and standard of identity prescribed for canned figs by § 145.130, except that in lieu of a packing medium specified in § 145.130(c), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

d. by revising § 145.136(a) to read as follows:

§ 145.136 Artificially sweetened canned fruit cocktail.

(a) Artificially sweentened canned fruit cocktail is the food which conforms to the definition and standard of identity prescribed for canned fruit cocktail by § 145.135(a), except that in lieu of a packing medium specified in § 145.135(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

e. By revising § 145.171(a) to read as follows:

§ 145.171 Artificially sweetened canned peaches.

(a) Artificially sweetened canned peaches is the food which conforms to the definition and standard of identity prescribed for canned peaches by § 145.170(a), except that in lieu of a packing medium specified in § 145.170(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

f. By revising § 145.176(a) to read as follows:

§ 145.176 Artificially sweetened canned pears.

(a) Artificially sweetened canned pears is the food which conforms to the definition and standard of identity prescribed for canned pears by § 145.175(a) except that in lieu of a packing medium specified in § 145.175(a)(3), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin and may contain any mixture of any edible organic salt or salts and any edible organic acid or acids as a flavor-enhancing agent, in a quantity not more than is reasonably required for that purpose.

* * * * *

g. By revising § 145.181(a) to read as follows:

§ 145.181 Artificially sweetened canned pineapple.

(a) Artificially sweetened canned pineapple is the food that conforms to the definition and standard of identity prescribed for canned pineapple by § 145.180(a), except that in lieu of a packing medium specified in § 145.180(a)(2), the packing medium used is water sweetened with one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter. Such packing medium may be thickened with pectin.

* * * * *

PART 150—FRUIT BUTTERS JELLIES, PRESERVES, AND RELATED PRODUS

2. In Part 150:

a. By revising § 150.141(c) to read as follows:

§ 150.141 Artificially sweetened fruit jelly.

* * * * *

(c) The artificial sweetening ingredients referred to in paragraph (a) of this section are one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter.

* * * * *

b. By revising § 150.161(c) to read as follows:

§ 150.161 Artificially sweetened fruit preserves and jams.

* * * * *

(c) The artificial sweetening ingredients referred to in paragraph (a) of this section are one or more of the artificial sweeteners listed in and complying with Parts 170 through 189 of this chapter.

* * * * *

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

3. In Part 172:

§ 172.135 [Amended]

a. By amending § 172.134 Disodium EDTA by deleting paragraph (b)(3).

b. By amending § 172.812 by revising paragraphs (b) and (c) to read as follows:

§ 172.812 Glycine.

* * * * *

(b) The additive is used or intended for use as a stabilizer in mono- and diglycerides prepared by the glycerolysis of edible fats or oils in an amount not to exceed 0.02 percent of the mono- and digylcerides.

(c) To assure safe use of the additive, in addition to the other information required by the act, the labeling of the additive shall bear adequate directions for the use of the additive in compliance with the provisions of this section.

§ 172.820 [Amended]

c. By amending § 172.820 Polyethylene glycol (mean molecular weight 200–9,500), by deleting and reserving paragraph (c)(2).

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS

§ 180.37 [Revoked]

4. In Part 180, by revoking § 180.37 Saccharin, ammonium saccharin, calcium saccharin, and sodium saccharin, which had permitted saccharin and its salts in food on an interim basis pending additional study.

PART 189—SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD

5. In Part 189, by adding new § 189.185 to read as follows:

§ 189.185 Saccharin and its salts.

(a) The food additive saccharin is the chemical, 1.2-benzisothiazolin-3-one-1, 1-dioxide ($C_7H_5NO_3S$). Ammonium saccharin, calcium saccharin, and sodium saccharin are produced by the additional neutralization of saccharin with the proper base to yield the desired salt. Saccharin and the named salts have been used as sweetening agents in food.

(b) Food containing any added saccharin or saccharin salt is deemed to be adulterated in violation of the act.

PART 310—NEW DRUGS

6. In Part 310, by adding new § 310.514 to read as follows:

§ 310.514 Saccharin; use as an ingredient in drug products.

(a) Saccharin has been used for many years as a flavoring agent in drug products, such as pediatric liquid oral preparations, cough sirups, chewable tablets, and toothpaste with medical claims. Saccharin has also been used in the management or mitigation diabetes and other conditions in which the available carbohydrate and/or calories of a patient must be controlled. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. The potential risk in humans outweighs the benefits of nontherapeutic use of saccharin. On the basis of this new evidence, saccharin has not been shown to be safe for use as an inactive drugs ingredient, with certain exceptions as provided for in paragraph (f) of this section.

(b) (1) Any drug product that contains saccharin, or one of its salts, as a single-active-ingredient product in liquid, tablet or powder form for use as a tabletop sweetener is a new drug within the meaning of seciton 201(p) of the act and requires an approved new drug application for marketing.

(2) Such products currently being marketed may remain on the market as over-the-counter products: *Provided,* (i) A new drug application complying with the requirements of § 314.1 of this chapter is submitted within 180 days of the date of publication of a final regulation; (ii) All products labeled after (120 days after date of publication of a final regulation) shall have the following statements displayed prominently on the principal display panel and on any other labeling, unless revised upon approval of the new drug application:

(A) "For use as a noncaloric sweetener when a sugar-restricted diet is medically indicated, as in patients with diabetes."

(B) "Warning: Saccharin causes bladder cancer in animals. Use of saccharin may increase your risk of cancer."

(C) Any drug product that contains saccharin as an inactive ingredient is a new drug within the meaning of section 20(p) of the act and is misbranded and subject to regulatory action under sections 301, 502, and 505 of the act.

(D) Any holder of an approved new drug application for a drug product containing saccharin as an inactive ingredient shall submit to the Food and Drug Administration on or before (9 months after date of publication of final regulation) a supplemental application providing for a revised formulation removing saccharin as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iii) Data to establish that the stability of the product is not adversely affected by the revised formulation. If the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(A) To test the stability of marketed batches at reasonable intervals;

(B) To submit the data as they become available; and

(C) To recall from the market any batch found to fall outside the approved specifications for the drug.

(2) The revised formulation shall not be marketed before the receipt of written notice of approval of the supplement by the Food and Drug Administration.

(c) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a drug product containing saccharin as an inactive ingredient shall amend the IND notice before (9 months after date of publication of final regulation) to provide for a revised formulation removing saccharin as an ingredient.

(f) If the holder of an approved new drug application or sponsor of an IND notice fails to comply with the provisions of paragraph (d) or (e) of this section, the Commissioner will initiate action to withdraw approval of the application or terminate the IND notice in accordance with the applicable provisions of section 505 of the act and Parts 312 and 314 of this chapter.

(g) Any person may file a petition in accordance with Part 10 of this chapter to amend paragraph (c) of this section to specify a use of saccharin in a drug product as not being subject to the misbranding provisions of that paragraph. The petition must be supported by the following information:

(1) The amount of saccharin contained in each dose of the drug;

(2) An adequate showing that there are not technically feasible alternatives to the use of saccharin in the drug product, or an adequate showing that the drug product provides a substantial health benefit or other public benefit that would not be available without the use of saccharin; and

(3) A copy of the proposed labeling clearly specifying the saccharin content and its intended use.

PART 430—ANTIBIOTIC DRUGS; GENERAL

7. In Part 430, by adding new Subpart F—Ingredients No longer Shown To Be Safe, consisting at this time of § 430.300, to read as follows:

Subpart F—Ingredients No Longer Shown To Be Safe

§ 430.300 Saccharin; use as an ingredient in antibiotic drug products.

(a) Saccharin has been used for many years as a flavoring agent in drug products, such as pediatric liquid oral preparations, cough sirups, chewable tablets, and toothpaste with medical claims. Saccharin has also been used in the management or mitigation of diabetes and other conditions in which the available carbohydrate and/or calories of a patient must be controlled. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and has a potential for causing cancer in humans. The potential risk in humans outweighs the benefits of nontherapeutic use of saccharin. On the basis of this new evidence, saccharin has not been shown to be safe for use as an inactive drug ingredient, with certain exceptions as provided for in paragraph (e) of this section.

(b) (1) Any manufacturer or other person who holds an approved antibiotic drug file providing for a product that contains saccharin shall sumbit an amendment on or before (9 months after date of publication of final regulation) providing for a revised formulation removing saccharin as an ingredient.

(2) The amendment shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iii) Data to establish that the stability of the product is not adversely affected by the revised formulation. If the data are too limited to support a conclusion that the drug will retain its declared potency for the period allowed by the expiration date, a commitment from the applicant:

(A) To test the stability of marketed batches at reasonable intervals;

(B) To submit the data as they become available; and

(C) To recall from the market any batch found to fall outside the approved specifications for the drug.

(c) No batch of antibiotic drug product containing saccharin as an ingredient will be certified or released after (18 months after date of publication of final regulation).

(d) (1) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a drug product containing saccharin as an ingredient shall amend the IND notice before (9 months after date of publication of final regulation) to provide for a revised formulation removing saccharin as an ingredient.

(2) If the sponsor of an IND notice fails to comply with the provisions of paragraph (d) (1) of this section, the Commissioner will initiate action to terminate the IND notice in accordance with the applicable provisions of section 507 of the act and Parts 312 and 433 of this chapter.

(e) Any person may file a petition in accordance with Part 10 of this chapter to amend paragraph (c) of this section to specify a use of saccharin in a

drug product which justifies certification or release of the product. The petition must be supported by the following information:

(1) The amount of saccharin contained in each dose of the drug;

(2) An adequate showing that there are no technically feasible alternatives to the use of saccharin in the drug product, or an adequate showing that the drug product provides a substantial health benefit or other public benefit that would not be available without the use of saccharin; and

(3) A copy of the proposed labeling clearly specifying the saccharin content and its intended use.

PART 510—NEW ANIMAL DRUGS

8. In Part 510, by adding new § 510.414, to read as follows:

§ 510.414 Saccharin.

(a) There are no approved or documented uses of saccharin as an ingredient in animal drugs intended for use in food-producing animals. Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. In food-producing animals, the use of saccharin as an ingredient in animal drugs or animal feed requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act if it is a carcinogen, or by an assay designated in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist. On the basis of this evidence, saccharin has not been shown to be safe for use as an inactive ingredient in animal drugs intended for use in food-producing animals.

(b) Saccharin has been used as an ingredient in some animal drugs intended for use in non-food-producing animals. Saccharin provides no therapeutic benefit to animals and has not been shown to provide any overriding benefit to a measurable animal treatment population. For these reasons, the Commissioner concludes that any risks to animals from the use of saccharin in such drugs outweigh any theoretical benefit alleged from its continued use. Accordingly, on the basis of the new evidence, saccharin has not been shown to be safe for use as an active or inactive ingredient in animal drugs intended for use in non-food-producing animals.

(c) Any drug product that contains saccharin as an inactive ingredient is a new animal drug within the meaning of section 201(w) of the act, and is unlawful and subject to regulatory action under sections 301 and 512 of the act.

(d) Any holder of an approved new animal drug application for a drug product containing saccharin as an inactive ingredient shall submit to the Food and Drug Administration on or before (9 months after date of publication of final regulation) a supplemental application providing for a revised formulation removing saccharin as an ingredient.

(e) If the holder of an approved new animal drug application fails to comply with the provisions of paragraph (d) of this section, the Commissioner will initiate action to withdraw approval of the application in accordance with the applicable provisions of section 512 of the act.

PART 589—SUBSTANCES PROHIBITED FROM USE IN FOOD OR FEED FOR ANIMALS OTHER THAN MAN

9. By adding a new Part 589, consisting at this time of § 589.185, to read as follows:

§ 589.185 Saccharin and its salts.

(a) The food additive saccharin is the chemical, 1,2-benzisothiazolin-3-one-1,1-dioxide ($C_7H_5NO_3S$). Ammonium saccharin, calcium saccharin, and sodium saccharin are produced by the additional neutralization of .saccharin with the proper base to yield the desired salt. Saccharin and the named salts have been used as sweetening agents in human food and may have been used as a sweetening agent in food or feed for animals other than man.

(b) Information now available demonstrates that saccharin causes malignant bladder tumors in test animals and therefore has a potential for causing cancer in humans. For this reason it has not been shown to be safe for use in food or feed for animals other than man. In food-producing animals, the use of saccharin as an ingredient in animal feed requires a demonstration that no residue will be found in food from the edible products derived from those animals, either by an assay designated in accordance with the provisos to the anticancer clauses of the act if it is a carcinogen, or by an assay designated in accordance with the general safety provisions of the act. No such assay has been submitted, nor, to the knowledge of the Commissioner, does such an assay exist.

(c) Food or feed for animals other than man containing any added saccharin or saccharin salt is deemed to be adulterated in violation of the act.

PART 700—GENERAL

10. In Part 700, by adding a new § 700.22, to read as follows:

§ 700.22 Use of saccharin as an ingredient in cosmetic products.

(a) Saccharin and its salts have been used as an ingredient in cosmetic products. The ingestion of saccharin has been shown to induce cancer of the bladder in rats. The Commissioner concludes that, on the basis of these findings, saccharin is a deleterious substance that may render injurious to users any cosmetic product that contains saccharin or a saccharin salt as an ingredient and is likely to be ingested under normal conditions of use.

(b) Any cosmetic product containing saccharin or a saccharin salt as an ingredient that is likely to be ingested is deemed to be adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

Interested persons may, on or before June 14, 1977, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857, written comments (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. The envelope containing the comment(s) should be prominently marked "SACCHARIN." Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document contains a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A–107 and certifies that an inflation impact statement has been prepared. A copy of the inflation impact statement is on file with the Hearing Clerk, Food and Drug Administration.

Dated: April 12, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.77–11139 Filed 4–14–77;8:45 am]

[21 CFR Parts 145, 150, 172, 180, 189, 310, 430, 510, 589 and 700]

[Doc. No. 77N–0085]

SACCHARIN AND ITS SALTS

Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice of Public Hearing.

SUMMARY: The Commissioner of Food and Drugs announces that a public hearing will be held on May 18 and 19, 1977 to receive information and views from interested persons on the proposed regulations regarding saccharin published elsewhere in this issue of the FEDERAL REGISTER.

DATES: The public hearing will be held on May 18 and 19, 1977 at 9 a.m. A written notice of participation must be filed by May 9, 1977.

ADDRESSES: Written notices of participation should be sent to the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Mr. Ted Herman, Compliance Regulations Policy Staff (HFC–10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857 (301–443–3480).

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is proposing to revoke the interim food additive regu-

lation, 21 CFR 180.37 (formerly 21 CFR 121.4001, prior to recodification published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302)) under which saccharin and its salts (saccharin) are currently permitted as ingredients in prepackaged food such as soft drinks, and as tabletop nonnutritive sweeteners. The Commissioner is also proposing to accept and promptly review new drug applications for the marketing of saccharin as a single-ingredient drug, available without a physician's prescription. The Commissioner is also proposing to prohibit the use of saccharin in cosmetics that are likely to be ingested, to amend the standards of identity that provide for the use of saccharin, and to prohibit the use of saccharin in animal drugs and animal feed. Comments on the proposal may be submitted until June 14, 1977. Because of the broad public interest in and concern about saccharin, the Commissioner has determined that, in addition to the normal 60-day comment period for receipt of written comments, an informal public hearing should be held regarding the proposal. The purpose of the informal hearing is to provide an open forum for the presentation of information and views concerning all aspects of the proposal by interested persons, be they consumers, scientists, or representatives of manufacturers of regulated products.

In preparing a final regulation, the Commissioner will consider the administrative record of this hearing along with all other written comments received during the comment period specified in the proposal.

The hearing will be held on May 18 and 19, 1977 in the auditorium located on the first floor in the HEW North Building, 330 Independence Ave. SW., Washington, DC 20201. The hearing will begin at 9 a.m. each day. The presiding officer will be Dr. Donald Kennedy, Commissioner of Food and Drugs.

A written notice of participation must be filed pursuant to 21 CFR 12.45 (formerly 21 CFR 2.131 prior to recodification published in the FEDERAL REGISTER of March 22, 1977 (42 FR 15553)) with the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857 not later than May 9, 1977. The envelope containing the notice of participation should be prominently marked "Saccharin Hearing." The notice of participation itself must contain the Hearing Clerk Docket No. 77N–0085, the name, address, and telephone number of the person desiring to make a statement, along with any business affiliation, a summary of the scope of the presentation, and the approximate amount of time being requested for the presentation. A schedule for the hearing will be mailed to each person who files a notice of participation; the schedule will also be available from the FDA Hearing Clerk. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations.

In the event that the responses to this notice of hearing are so numerous that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the Commissioner will allocate the available time among the persons making the oral presentation to be used as they wish. Formal written statements (preferably in quadruplicate) may be presented to the presiding officer on May 18 and 19 for inclusion in the administrative record.

The hearing will be open to the public. Any interested person who files a written notice of participation may be heard with respect to matters relevant to the issues under consideration.

Dated: April 12, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc.77–11138 Filed 4–14–77;8:45 am]